Contingency INDs for Force Health Protection: Ethical Challenges

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Background

- Fall of 2002: Impending war in Iraq
  - Stated rationale was removal of WMD
- Many CW & BW countermeasures are not FDA licensed products
  - IND status
  - History of events since ODS in 1991
- Need for new / updated contingency protocols

OEF/OIF CW / BW Threats & Contingency Protocols

- Nerve Agents (Soman)
  - Pyridostigmine bromide (PB)
- Variola (smallpox)
  - Prevention
    - Licensed (Dec 02) Dryvax® vaccine (full strength)
    - Investigational use of Dryvax® 1:5 dilution
  - Treatment
    - Immune globulin
    - Cidofovir

OEF/OIF CW / BW Threats & Contingency Protocols

- Treatment Protocols
  - Vaccinia (smallpox vaccine) adverse reactions
    - Immune serum globulin
    - Cidofovir
  - Anthrax
    - Post-exposure use of antibiotics +/- vaccine

OEF/OIF CW / BW Threats & Contingency Protocols

- Botulinum toxin
  - Prevention:
    - Human pentavalent immune globulin
    - Pentavalent botulinum toxoid vaccine
  - Treatment:
    - Equine heptavalent immune globulin

Prevention vs. Treatment

Prevention Protocols	Treatment Protocols
Controlled	Uncontrolled
Standard of care and research	Standard of care
Written IC possible	IC not possible
Can be accomplished by a dedicated clinical trials team	Must be given by organic medical assets

Prevention Interventions

- Clinical "trials" can be controlled in small numbers (N < 250)
- Must have dedicated, experienced team
- IC can be done right

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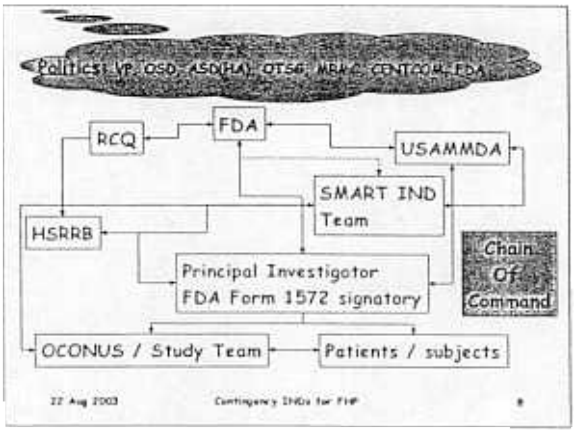

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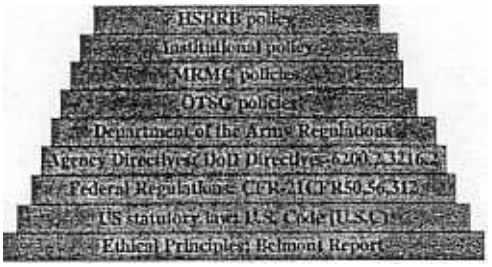
Hierarchy of Control



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Belmont Principles

- Respect for Persons
  - Informed consent
- Beneficence - an obligation to...
  - 1) do no harm
  - 2) maximize benefits & minimize harm
- Justice

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Boundaries Between Practice and Research

- "It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success."
- "By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge"

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OIF Contingency Protocols

- Goal was providing standard of medical care to injured soldiers = NOT research
  - Bot toxin - E-BAT, vaccine, HBIG
  - Variola - ISG

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Specific Issues

- DoDD 3216 vs. 6200
- Eligibility criteria for Rx protocols
- IC dilemmas for Rx protocols
- EPWs
- Medical Monitor

DoDD 3216.2 (25 Mar 2002)

- SUBJECT: Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research
- 2. Applicability and Scope:
- 2.3. Does not apply to the use of investigational new drugs, biological products, or devices for purposes of Force Health Protection. Such use is not research and is governed by DoD Directive 6200.2 (reference (d)).

DoDD 6200.2 (1 Aug 2000)

- 3. DEFINITIONS
- 3.1. Force Health Protection. An organized program of healthcare preventive or therapeutic treatment, or preparations for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions.

DoDD 3216 vs. 6200 ?

- Do we throw out 3216 for FHP?
- 6200 deals with waiver of IC under 10 USC 1107
  - This will never happen (politics!)
- 6200 requirement to execute a protocol "under all applicable rules and regulations"

6200.2 Requirements

- 4.2.2. The Secretary of the Army, as Executive Agent, in concert with the Commander of the Combatant Command involved and the ASD(HA), shall develop a specific treatment protocol for use of the IND.
- The protocol shall:
  - comply with 21 CFR Part 312
  - be approved by the HSRRB
  - Approved by the FDA
  - Provide for prior informed consent of members receiving the IND consistent with 21 CFR Part 50

IC and use of E-BAT in a botulinum toxin mass casualty

- Who can we treat?
- Selection criteria stated in section 5.1 are:
- "For this emergency use protocol, service members include all U.S. military forces, government employees, contractors, family members, allied forces, and local nationals."

IC and use of E-BAT in a botulinum toxin mass casualty

- Approved protocol provided a list of eligible persons / categories
- No mention of children

Bot toxin mass casualty and the use of E-BAT

- Approved protocol had 41 pages of consent / assent documents (in triplicate)
- 21 CFR § 50.23 (a)(b)(c) Exception from general requirements.
- Consideration for use of 50.23 (d)

Informed Consent: 21 CFR 50.23 - Emergency use

IC cannot be obtained because

- Inability to communicate
- Inability to obtain legally effective consent from patient
- Not sufficient time to obtain legally effective consent from the patient's legal representative
- Independent MD provides written certification

DoDD 6200.2 (1 Aug 2000)

4.9. INDs for Non-military Personnel. In any case in which an IND is used for force health protection for military personnel and subject to the same health risk are Emergency-Essential civilian employees (reference (e)) and contractor personnel performing essential contractor services (reference (f)) in conjunction with the military mission, the IND shall be available for protection of these non-military personnel under the same terms and conditions, except that the authority to waive informed consent under references (a) through (c) is inapplicable to these personnel.

EPWs?

- Can we use E-BAT to treat EPWs / local nationals, children (vulnerable populations) in a mass casualty ?
- Clear moral, ethical, and medical rationale to offer E-BAT to any who would benefit.

DoDD 3216.2 (25 Mar 2002)

- 4.4. Additional Protections for Certain Categories of Research. In addition to the requirements of reference (c), the following requirements apply to research involving certain subjects or purposes.
- 4.4.2. The involvement of prisoners of war as human subjects of research is prohibited.

Additional E-BAT IC issues

English language IC docs
- Multiple other languages possible
- No translators available

Parental consent for minors

Prioritization of use in mass cal with limited product
- Who gets treated - us or them?

Medical Monitor

DoD unique requirement IAW section 4.4.3 of DODD 3216.2 (25 March 2002) for greater than minimal risk research.
- Independent MM by name
- Individual patient management & safety
- Serve as patient advocate
- Report directly to the IRB of record (HSRRB)
- MM authorized to stop study

However, 3216 not applicable for FHP protocols!

No requirement for MM for FHP protocols?

Results of OIF deployment

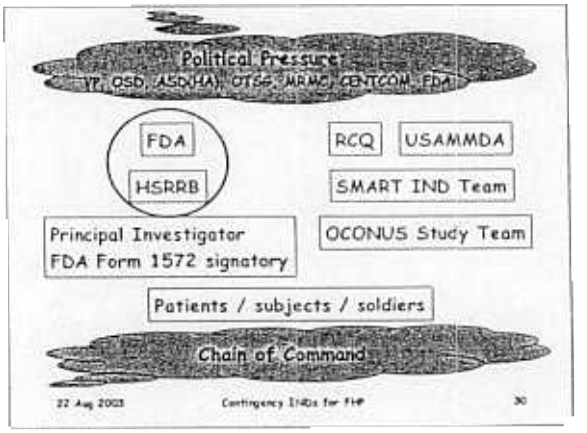
- Contingency protocols used in OIF were conducted IAW with accepted clinical trials guidelines
- IND product status guarantees we cannot achieve FHP
- IND status of accepted standard of care products (E-BAT) would have denied life saving care to soldiers in the event of the use of bot toxin

Issues for the next time

- Clarify 6200 vs. 3216
- Are contingency protocols research... or not?
- Differentiate between Px and Rx protocols
- Eliminate IC & MM requirement when possible for Rx protocols

Specific Recs to HSRRB

- Don't approve a contingency protocol unless...
  - Qualified PI identified
  - Written assurance from combatant commander that PI will have resources, authority and support to fulfill FDA 1572 requirements



DEPARTMENT OF THE ARMY
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HEADQUARTERS, UNITED STATES ARMY MEDICAL RESEARCH
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REPLY TO
ATTENTION OF

MCMR-JA

18 March 2003

MEMORANDUM FOR Commander, US Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, MD 21702

SUBJECT: Using INDs to Treat Symptomatic Enemy Prisoners of War

1. Purpose: This Memorandum responds to a 15 March 2003 inquiry from a member of the IND team assigned to the CFLCC Surgeon, concerning our 4 March 2003 opinion, SUBJECT Clarification of Eligibility Criteria for HSRRB Contingency Protocol Log A-12007, Heptavalent Equine-Based Botulinum Antitoxin (E-BAT)

2. Issue: E-BAT is an IND treatment for patients with early symptoms of botulinum toxin poisoning. The CFLCC Surgeon staff is concerned that treating enemy prisoners of war (EPWs) who are symptomatic of botulism poisoning with E-BAT may conflict with the prohibition in DoDD 3216.2 against using EPWs as research subjects.

3. Conclusion: The proposed use of E-BAT to treat symptomatic EPWs is not medical research subject to the prohibition of DoDD 3216.2. Rather, this proposed use of E-BAT constitutes emergency medical care as authorized by 21 CFR 50.25(d) and DoDD 6200.2 and would constitute the standard of care for our forces in the theater. Such emergency medical care is consistent with our obligation under Articles 10 and 11 of Protocol I to the Geneva Conventions of 1949 to provide medical care to EPWs as required by their condition, consistent with generally accepted medical standards which would be applied under similar medical circumstances to members of our own force. Thus, treating symptomatic EPWs with E-BAT, even without informed consent, may be accomplished pursuant to 21 CFR 50.23(a)-(c). I have coordinated this opinion with the MEDCOM SJA.

4. Discussion

a. Application of DoDD 3216.2. DoDD 3216.2, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Sponsored Research," at para. 4.4.2, prohibits using prisoners of war in medical research, but does not apply to the intended use of E-BAT. The regulation states at para. 2.3 that it does not apply to the use of investigational new drugs, biological products, or devices for purposes of Force Health Protection. The regulation states such use is not research and falls instead within DoDD 6200.2, "Use of Investigational New Drugs for Force Health Protection." The prohibition against using EPWs in medical research would apply if the command were seeking to enroll EPWs in an IND research protocol, but that is not the command's intent, nor purpose. The command intends to deploy E-BAT in the theater for force health protection. This intent removes E-BAT and related INDs for force health protection from the coverage of DoDD 3216.2 by its own terms. Thus, the command would treat an EPW with the IND not to prove the efficacy of the IND or gather scientific

information, but in an effort to save the EPW from a life-threatening disease process, using the same treatment methods it intends to apply to symptomatic members of our own forces.

b. Application of DoDD 6200.2. The command has requested authority to deploy E-BAT as a force health protection measure under DoDD 6200.2. EPWs are not explicitly included in the regulatory definition of Force Health Protection at para. 3-1, DoDD 6200.2: "An organized program of healthcare preventive or therapeutic treatment, or preparation for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions." Arguably, EPWs fall within the definition's umbrella term "military personnel," as they enjoy protected status under Protocol I to the Geneva Conventions because of their military status. This protected status, in turn, entitles them to medical care required by their condition and consistent with the standard of care provided our own forces. This analysis would authorize treating symptomatic EPWs with INDs as an authorized force health protection measure. Alternatively, and without having to address the issue of whether EPWs ought to be considered members of the force, DoDD 6200.2 includes authority for providing standard of care treatment at para. 2.3 as follows: "[The regulation] Does not apply to actions by DoD healthcare providers that are within standard medical practice in the United States and are not subject to FDA regulations [governing clinical research using INDs]." This provision recognizes that DoD healthcare providers are authorized to apply measures necessary and appropriate according to standard medical practice in the U.S., without regard to other requirements of the Force Health Protection IND regime. Thus, DoDD 6200.2 authorizes our healthcare providers to provide U.S. standard of care treatment to EPWs.

c. Application of FDA Clinical Research Regulations. A treating physician is not limited by the FDA clinical research regulations in providing emergency medical care consistent with other applicable law. The FDA regulations themselves at 21 CFR 50.25(d) expressly state that "Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local law." Similarly, the informed consent provisions of 21 CFR 50.23 do not make a distinction between the anticipated categories of subjects and others who are in a life-threatening situation. Thus, FDA regulations authorize our healthcare providers to administer an IND for emergency care of symptomatic EPWs.

d. Application of U.S. Obligations under the Geneva Conventions. The command is obliged under Article 10 of Protocol I to the Geneva Conventions to respect and protect EPWs and provide them "to the fullest extent practicable and with the least possible delay, the medical care and attention required by their condition." Article 11 of Protocol I expands on this medical care obligation in para. 1 where it prohibits any medical procedure "which is not indicated by the state of health of the person concerned and which is not consistent with generally accepted medical standards which would be applied under similar medical circumstances to persons who are nationals of the Party conducting the procedure and who are in no way deprived of liberty." Article 11, para. 2(b) also prohibits medical or scientific experiments, even with the EPW's consent, unless the medical procedure involved meets the standards addressed in Article 11, para. 1, discussed in the preceding sentence. Applying these

standards to the use of E-BAT demonstrates that the command should make E-BAT available to EPWs in the same manner as members of our own forces. Use of contingency INDs in theater will be the standard of care and should be extended to EPWs. Article 11 of the Geneva Protocols at para. 5 gives EPWs the right to refuse any surgery, even when that surgery is the standard of care and endorsed by the treating healthcare provider. Our contingency IND treatment protocols are consistent with this concept of self-determination in that they provide for informed consent, unless the patient is unable to give consent. Where circumstances prevent informed consent, the provisions of 21 CFR 50.23 (a)-(c) engage and provide the healthcare provider an alternative mechanism for certifying the necessity for treating with an IND.

e. Case law Examining "Research" and Force Health Protection. Case law interpreting the 10 U.S.C. Section 980 prohibition against medical research involving military personnel absent informed consent supports our analysis that treating EPWs with this IND would not constitute prohibited medical research using prisoners. The District Court for the District of Columbia in Doe v. Sullivan, 756 F. Supp 12 (Dist. DC 1991), upheld a DoD decision to administer two INDs for force health protection against a challenge that such use violated a statutory prohibition against medical research absent informed consent. The court stated:

> "The DoD's use of unapproved drugs does not involve the type of scientific investigation under controlled circumstances that "research" connotes. On the contrary, the DoD has responded to very real circumstances and chosen what it views as the best alternative given current knowledge. . . .The fact that the DoD will collect information on the efficacy of the drugs does not transform the strategic decision to use the unapproved drugs in combat into research."

This same analysis applies with the same result to the current plan to use INDs for force health protection. Neither the DoD, nor courts asked to review the issue consider this use to constitute research and the FDA regulatory provisions discussed earlier contemplate use of INDs for emergency medical treatment outside clinical research. Thus, all these sources of legal authority concur that the proposed use of INDs for treating symptomatic EPWs is not research.

5. Recommendation. I recommend that the deployed command coordinate this issue with the command PAO and notify the ICRC of its intent to offer treatment with INDs to symptomatic EPWs, explaining the regulatory authority behind making this treatment available to our forces and demonstrating that this treatment will be the standard of care for our forces in theater.

WILLIAM D. PALMER
LTC, JA
Staff Judge Advocate

MEMORANDUM THRU HSSRB, MRMC, OTSG

FOR: ASD(HA

SUBJECT: Clarification of Eligibility Criteria for HSRRB Contingency Protocol Log A-12007; titled: "Emergency Use of Investigational Heptavalent Equine-Based Botulinum Antitoxin (Types A, B, C, D, E, F, and G) After Exposure to *Clostridium botulinum* or Other Closely Related Bacterial Species."

Investigational Heptavalent Equine botulinum antitoxin (E-BAT) is available for the treatment of patients with early symptoms of botulinum toxin poisoning under investigational new drug (IND) application BB-IND 10,621.

2 In the current (pending FDA approval) approved protocol, version 1.0, dated 01 Feb 03, the selection criteria stated in section 5.1 are:
"For this emergency use protocol, service members include all U.S. military forces, government employees, contractors, family members, allied forces, and local nationals."

3. In the event of deliberate use of botulinum toxin, it is possible that civilians and enemy prisoners of war (EPW) may be victims. According to the Geneva Convention and applicable international law, all combatants, including allied forces, as well as affected civilians, are to be considered equivalent in priority for utilization of available health care resources.

4 In addition, the current operational plan is to administer E-BAT in the Kuwait Armed Forces Hospital (KAFH) with back-up capacity in a civilian Kuwait hospital by CFLCC command authroities. It has been made very clear to the IND support team, offering a potentially life-saving intervention to US citizens and denying the same product to our Kuwait allies may not be a acceptable course of action and may jeopardize plans to utilize these facilities.

5. Informed consent materials are not currently available in regional native languages, such as Arabic or Kurdish. For an adult, informed consent could be waived under 21 CFR 50.24 or when possible, verbal consent with a translator IAW 21 CFR 50.27(b) may be feasible. For a minor, consent of a parent may not be possible. In any event, obtaining valid informed consent from local nationals in the setting of an intentional use of botulinum toxin will prove to be very difficult, if not impossible.

6. Use of a BW agent such as botulinum toxin will result in intense media coverage. Rapidly evolving events and very poor communications following use of a BW agent will result in a very confusing environment. If civilians or EPWs are victims, there will be enormous humanitarian and ethical pressure fueled by extensive media coverage to use any appropriate and available life saving intervention for non US personnel to include E-

BAT. Denying use of E-BAT in this setting based on US based regulatory concerns may prove difficult to justify.

6. The IND Support Team is requesting urgent clarification and guidance on the policy for personnel who may be treated with E-BAT. Please reply in writing to the following questions:

A. Are there any categories of persons based on age, national origin, affiliation with the US government or combatant status, which would not be eligible to receive E-BAT under the current approved protocol? In particular, we must know if the protocol allows for use of E-BAT in Kuwaiti civilians (any age), Iraqi civilians (any age), and Iraqi enemy prisoners of war (EPWs).

B. If there are categories of persons who are not eligible to receive this E-BAT under protocol A-12007, is there any mechanism by which CENTCOM chain of command can authorize use of an IND product, such as E-BAT, in vulnerable populations such as children, or very sensitive populations such as EPWs?

C. If CENTCOM can authorize use of E-BAT in persons not otherwise eligible, what level of command is required for such authorization?

D. We interpret the language in section 5.1 to be inclusive of all individuals. A specific statement that there are no categories of persons excluded would be very helpful. If this is not the intent of MRMC, OTSG, DoD, or the FDA, please provide immediate clarification. Exclusion of any persons will become a barrier to use in a mass casualty scenario.

E. Valid informed consent will be very difficult, or impossible, to obtain in any of the scenarios we envision. However, an attempt to do so with verbal translation, will be attempted. In the event translation capabilities are not available for civilian or EPWs, informed consent will be waived IAW 21 CFR 50.24. If this plan is not acceptable to the HSSRB, FDA, OTSG, or higher authorities, please provide immediate guidance.

Robert Kuschner, COL, MC
IND Support Team Leader